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The Cancer Control Challenge:
Better Understanding It to Better Face It

ASSOCIATION OF A GEOPROPOLIS EXTRACT WITH DOXORUBICIN AS A POTENTIAL TREATMENT STRATEGY FOR GASTRIC CANCER

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Introduction: Gastric Cancer (GC) is among the leading causes of cancer-related death worldwide. This scenario is driven not only by late diagnosis, but also by the limitations of existing therapies. Conventional chemotherapy is associated with high systemic toxicity, compromising patients' quality of life and, in some cases, limiting treatment continuity. Doxorubicin, for example, is a topoisomerase II inhibitor widely applied for various tumors, but its usage is often restricted due to severe side effects. Given these limitations, the development of safer, more selective and more effective therapies is urgently needed. In this context, natural products have emerged as promising sources of new antineoplastic molecules. Among them, geopropolis —a compound produced by stingless bees from plant resins, enzymatic secretions and soil or clay particles— is notable for its antioxidant, anti-inflammatory and antiproliferative effects, making it a promising alternative for new therapeutic approaches. **Objectives:** This study sought to assess the individual and combined effects of a geopropolis extract and doxorubicin in a GC cell model. **Methods:** For that, AGP01 cells (Metastatic Gastric Adenocarcinoma) and HEK-293 cells (Non-neoplastic Human Embryonic Kidney) were subjected to the MTT cell viability assay for 72 hours, with concentrations ranging from 100 to 1.56 µg/mL of the ethanolic geopropolis extract from the species *Melipona seminigra pernigra* (UBR) and ranging from 8 to 0.125 µM of doxorubicin, applied independently. Subsequently, the mean inhibitory concentration (IC50) of the extract was combined with the dosage curve of doxorubicin to investigate potential combination effects. Complementary analyses were also performed to evaluate the cell death pattern (Annexin V/PI), reactive oxygen species (ROS) production (DCFH-DA), and DNA damage (γH2AX), using both isolated and combined IC50 values. **Results:** We observed that the geopropolis extract reduced AGP01 cell viability with an IC50 of 8.3µg/mL, while doxorubicin showed an IC50 of 9µM. In HEK-293 cells, the geopropolis extract demonstrated lower toxicity (IC50 = 22.2 µg/mL), whereas doxorubicin was notably toxic (IC50 = 0.6 µM), indicating high selectivity for

the extract and low selectivity for the chemotherapy. The combination of both compounds led to a more pronounced reduction in cell viability, even at lower doxorubicin concentrations, suggesting a synergistic or additive effect. Both compounds individually induced apoptosis, and this effect persisted with the combination. When isolated, neither treatment influenced ROS levels, but their combination resulted in a significant decrease in ROS production, indicating potential antioxidant activity. DNA damage was accentuated with isolated doxorubicin treatment, while combination with the geopropolis extract mitigated this effect. **Conclusion:** In summary, the geopropolis extract demonstrated selective cytotoxic activity. When combined with doxorubicin, it enhanced treatment effectiveness, maintained apoptosis induction, reduced ROS levels and mitigated the genotoxicity caused by doxorubicin therapy. These results suggest that geopropolis may act as a possible adjunct agent, raising the efficacy and reducing the side effects of doxorubicin. However, further studies are needed to clarify its mechanisms of action and validate its applicability.

Keywords: Gastric Cancer; Geopropolis; Doxorubicin; Treatment.